Drug design package software

with in silico drug discovery

MolDesk Init

Ver.1.1.105

Quick Manual

IMSBIO Co., Ltd.

Table of Contents

1. Removal of functional limitations

MolDesk Init is a limited version of MolDesk Basic with some limited functionality.
The restricted functions are as follows

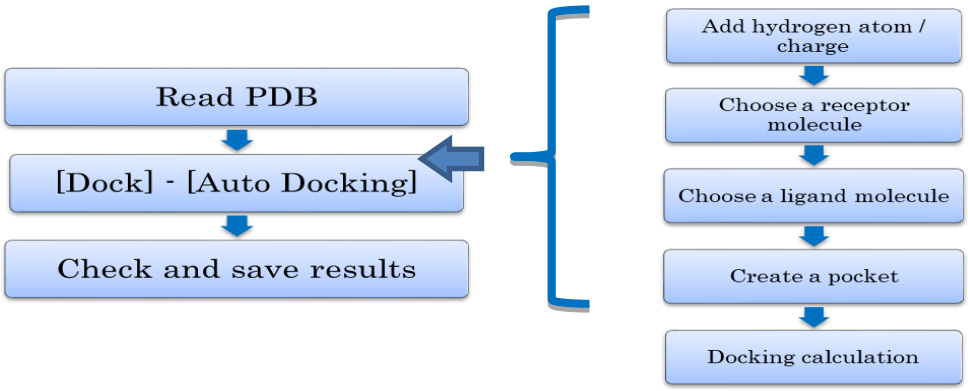
* The molecular weight of compounds (ligands) for which docking calculations can be performed is limited to **400 Da**.
* The total number of atoms in the system for MD calculations is limited to **30,000 atoms**.

If you want to remove these limitations, please consider MolDesk Basic or MolDesk Screening by IMSBIO Co., Ltd.

* IMSBIO Co., Ltd. https://www.imsbio.co.jp/
* MolDesk https://www.moldesk.com/
* MolDesk EC shop https://moldesk.official.ec/

2. MD Calculations

For the Windows version, MD calculations (molecular dynamics calculations) with GROMACS can be performed with a few clicks of the mouse.
The following is an example of the simplest automated MD calculation.
The procedure is as follows.



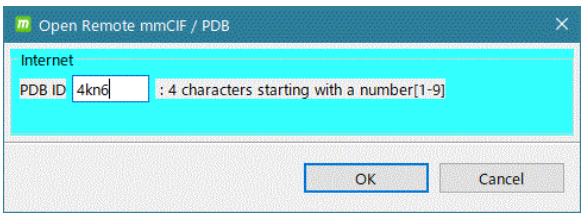
2.1. Molecular Input

If you are connected to the Internet, click the [PDB] or [TEST] button on the top page.

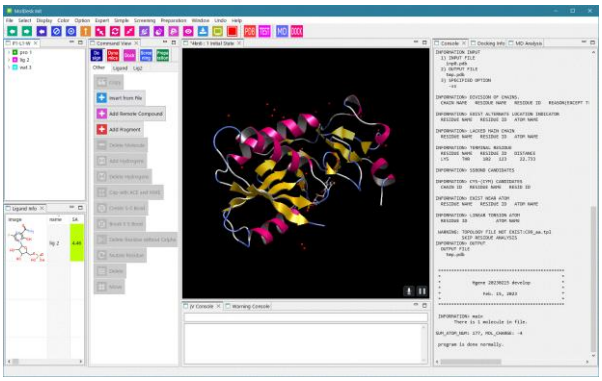
Each has the following functions.

[PDB]: Input the molecule of the PDB ID specified by the user.

[TEST]: Input molecules with any PDB ID 4kn6.



When the [PDB] button is clicked, the screen shown in the figure is displayed, so enter 4kn6 and click [OK].



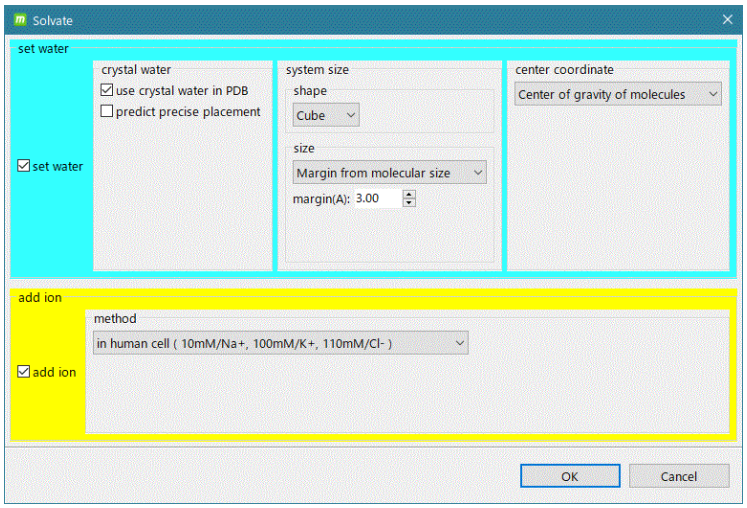
4kn6 will be entered.
The same applies when you click the [TEST] button.

* If you are not connected to the Internet, click [File] - [Open Molecular File] to load the sample / PDB / 4KN6.pdb file.

2.2. Automatic MD calculation

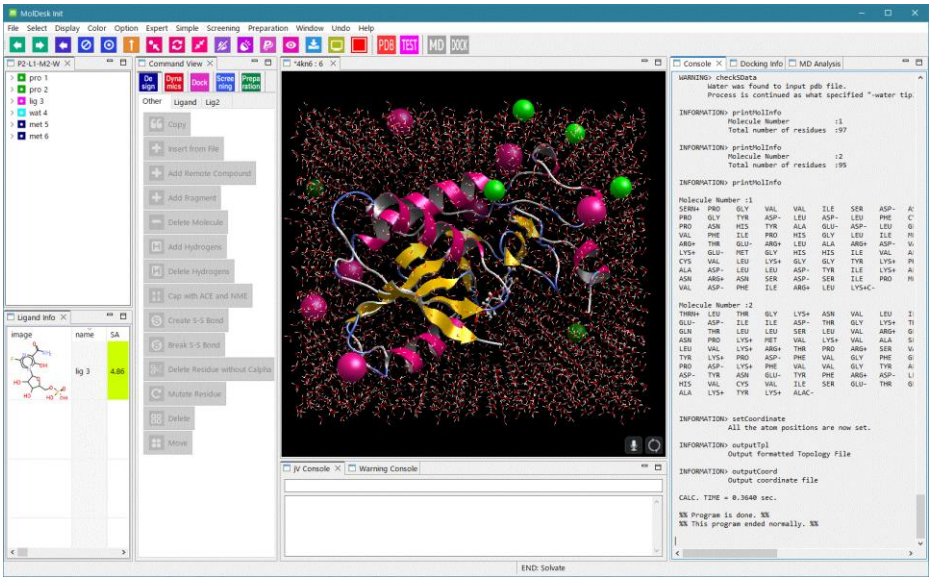
Next, click the [MD] button shown in the figure.
The process is performed in the following order.

* Add missing hydrogen atoms to all molecules (default is the dissociated state in water)
* Gasteiger charge added to all compounds or sugars
* Molecules other than compounds or sugars are charged based on the force field selected in [Help] - [Preference] - [Molecule] - [tplgeneX]



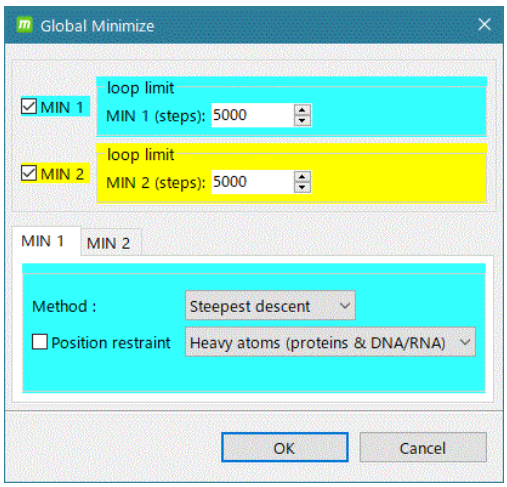
Displays a dialog box for selecting water solvents and ion addition methods.

Click the [OK] button.
The water solvents and ions are added.



Solvent: A rectangular box with the center of gravity of the system as the center of the solvent and a size of 3 Å from the solute boundary.

Ions: Na+, K+, and Cl- are added at the ion concentration of a human cell.



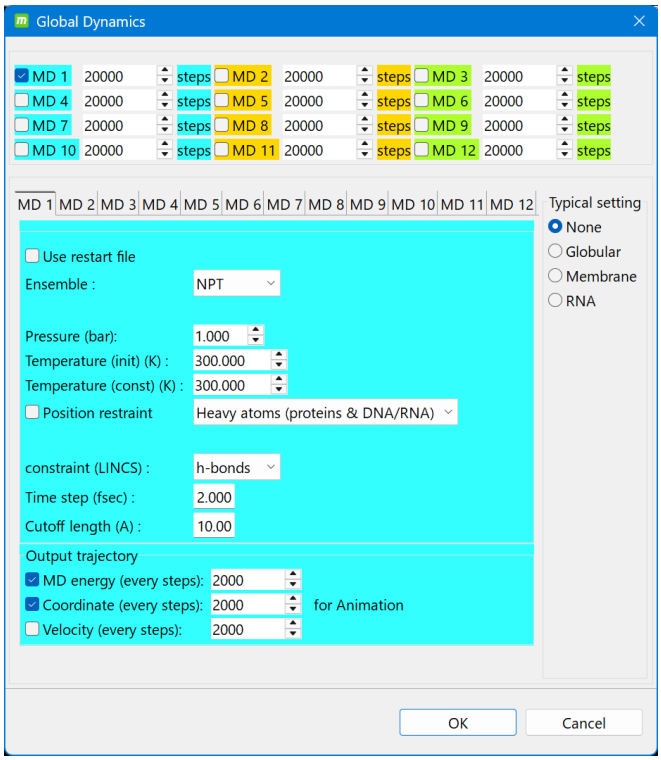
Click [OK] to display the dialog box for setting conditions for energy minimization calculations.

Two energy minimization calculations will be performed in succession.

The first one is the steepest descent method with 5000 steps. No position constraint

The second one is the conjugate gradient method, 5000 steps. No position constraint

When the energy minimization calculation is completed, the MD Calculation Condition Setting dialog box is displayed.



Click the [OK] button.

The MD calculation starts with the following conditions.

* Execute only once.
* The number of steps is 20000.
* NPT ensemble
* Pressure is 1 bar.
* Initial temperature 300K
* Constant temperature of 300K
* No position constraint
* Constraints of LINCS: h-bonds
* Time step is 2.0 fsec
* Cutoff radius is 10.0 Å.
* Energy file output (every 2000 steps)
* Trajectory file output (every 2000 steps)

This completes the entire process of calculating MD for molecules in aqueous solution.

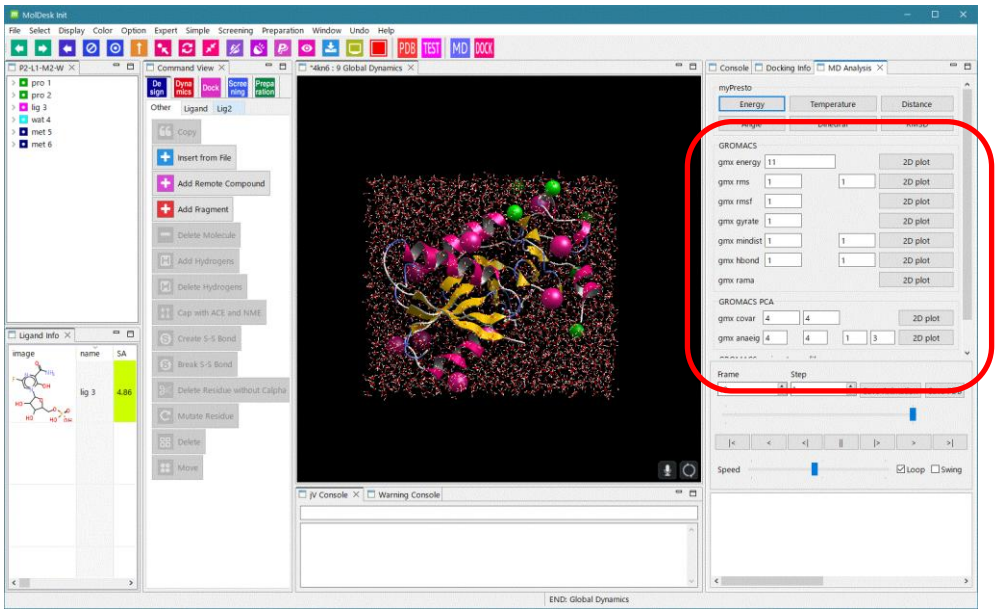
* The force field is set by default to AMBER GAFF2 for compounds or sugars and AMBER ff99SB for others (e.g. proteins).
  (Force field can be changed by [Help] - [Preference] - [Molecule] - [tplgeneX])

* The [MD] button is equivalent to the Dynamics [Dynamics] - [Auto Solvate and Dynamics] button.

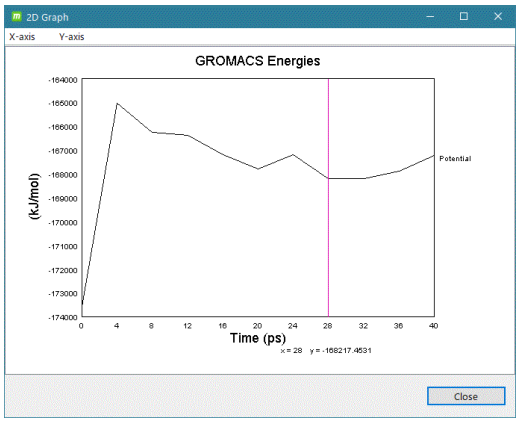
2.3. Trajectory Analysis

2.3.1. When MD calculation is performed in GROMACS

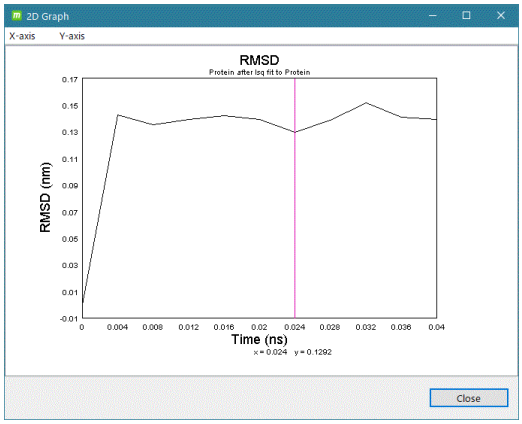
Click the [2D plot] button to run the trajectory analysis in GROMACS and display a graph with time axis linked to the movie.



gmx energy



gmx rms



Executable gmx commands

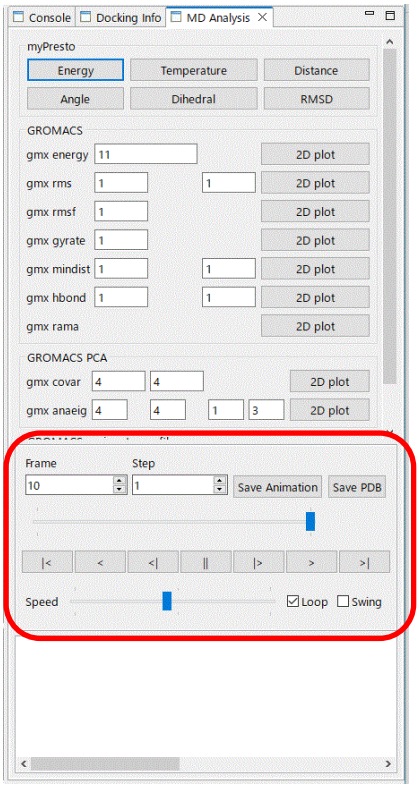
General	PCA Analysis
(1) gmx energy	(8) gmx covar
(2) gmx rms	(9) gmx anaeig
(3) gmx rmsf	
(4) gmx gyrate	
(5) gmx mindist	
(6) gmx hbond	
(7) gmx rama	

* For details on usage, please refer to the MolDesk Basic manual.
* For details on trajectory analysis with GROAMCS, refer to the GROMACS manual.

2.3.2. MD calculation by other than GROMACS

* For details on usage, refer to the MolDesk Basic manual.

2.4. 3D Animation Display and File Output



By operating the Animation controller on the MD Analysis screen, you can animate the time variation of atom movement (trajectory) on the 3D screen.

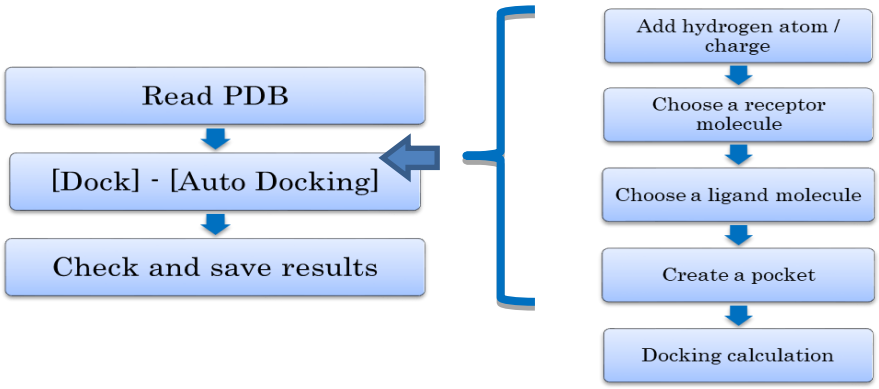
Click the [Save Animation] button to output the animation as a GIF file. The frame time interval can also be set.

Click the [Save PDB] button to save a snapshot of all trajectories in a PDB file.

3. Docking calculations

The following is an example of the simplest docking calculation performed by automation.

The procedure is as follows.



* Docking to nucleic acid molecules in addition to proteins is available in ver. 1.1.78 and later. Proteins or nucleic acid molecules can be specified as acceptors.

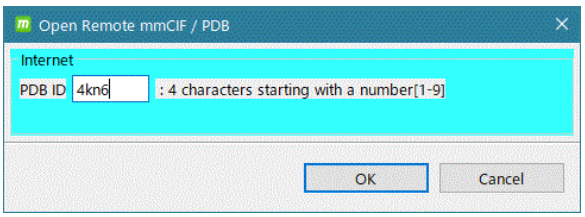
3.1. Molecular Input

If you are connected to the Internet, click the [PDB] or [TEST] button on the top page.

Each has the following functions.

[PDB]: Input the molecule of the PDB ID specified by the user.

[TEST]: Input molecules with any PDB ID 4kn6.



When the [PDB] button is clicked, the screen shown in the figure is displayed, so enter 4kn6 and click [OK].

4kn6 will be entered. The same applies when you click the [TEST] button.

* If you are not connected to the Internet, click [File] - [Open Molecular File] to load the sample / PDB / 4KN6.pdb file.

3.2. Automatic docking

Next, click the [DOCK] button in Fig.
The process is performed in the following order.

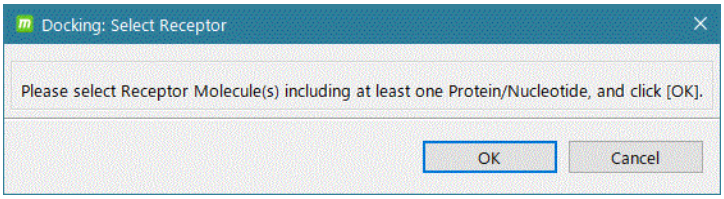
* Adds a missing hydrogen atom to all molecules (default is the dissociated state in water).
* Add Gasteiger charge for all compounds or sugars
* For molecules other than compounds or sugars, add charges based on the force field selected in [Help] - [Preference] - [Molecule] - [tplgeneX]

* The [DOCK] button is equivalent to 

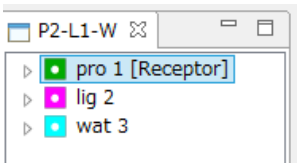
[Dock] -  [Auto Docking].

3.2.1. Select receptor and ligand molecules

A message dialog will appear prompting you to select a receptor.



Select pro1 in the tree view screen and click OK.

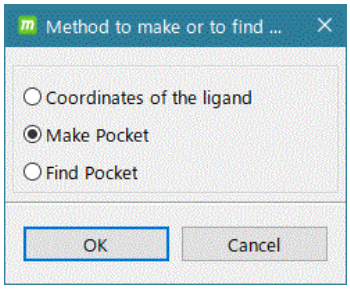


The notation of pro1 changes to pro1 [Receptor] because pro1 is recognized as a receptor.

* The receptor molecule must contain at least one protein or nucleic acid molecule. It may contain compounds, sugars or metals.

3.2.2. Create a pocket

After specifying the receptor, a dialog box will appear to select the pocket creation method.



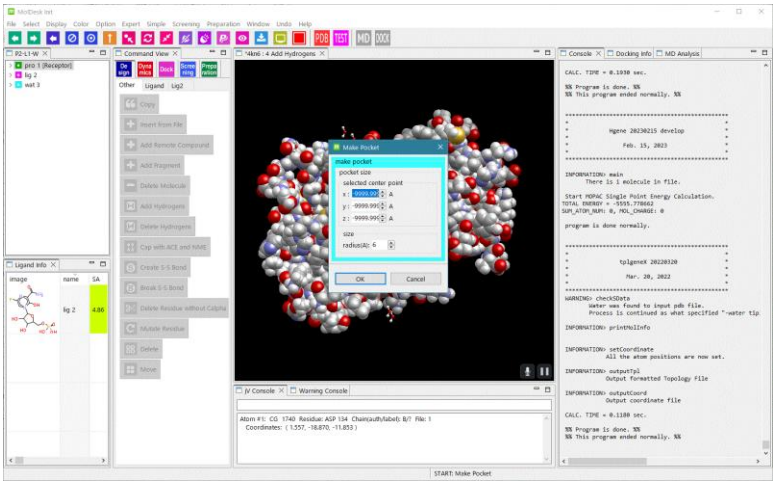
In this case, leave [Make Pocket] as it is and click [OK].

The following is a description of the items in the dialog box for selecting the pocket generation method.

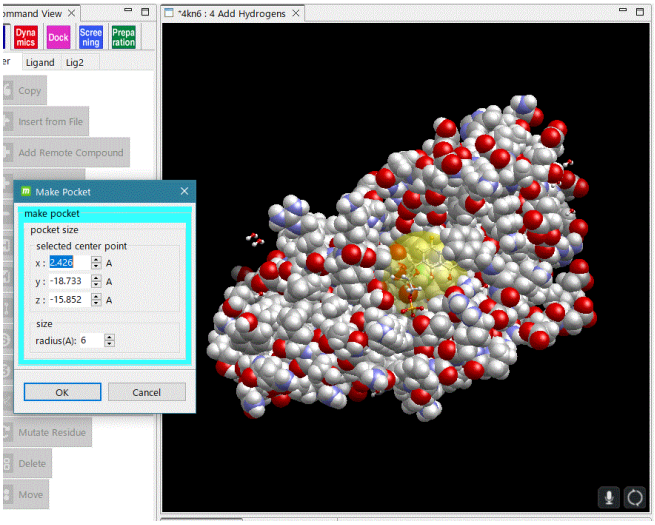
Item	Item
[Coordinates of the ligand]	The coordinates of the selected molecule are used as the probe point for the pocket. Multiple molecules other than protein or nucleic acid molecules can be selected and batch probed.
[Make Pocket]	Places a pocket sphere on the surface of the selected receptor and generates a pocket probe point inside the sphere.
[Find Pocket]	Performs a pocket search on the surface of the selected receptor and automatically generates multiple probe points in score order.

* For details on usage, please refer to the MolDesk Basic Manual.

The protein becomes a space-fill display model and displays a pocket selection dialog.

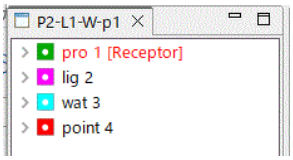


Click around the ligand molecule in the 3D screen.

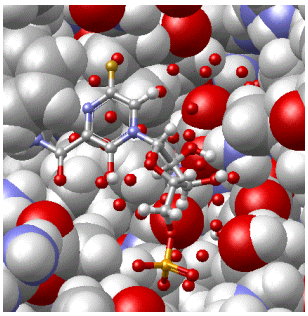


The selected pocket is displayed as a yellow translucent sphere.

Click the [OK] button.

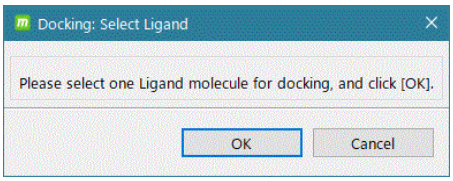


Display point4 in the tree view screen,



Add the probe points (red points) of the pocket in the yellow translucent sphere.

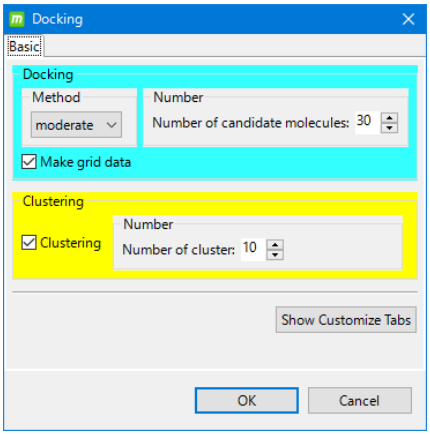
A message dialog prompting the user to select a ligand is displayed.



In this example, lig2 is selected in the tree view screen and [OK] is clicked.

3.2.3. Docking execution

A dialog box for setting the conditions for docking calculations appears.



In this example, leave the default conditions as they are and click OK. The docking calculation is executed.

All docking calculations are now complete.

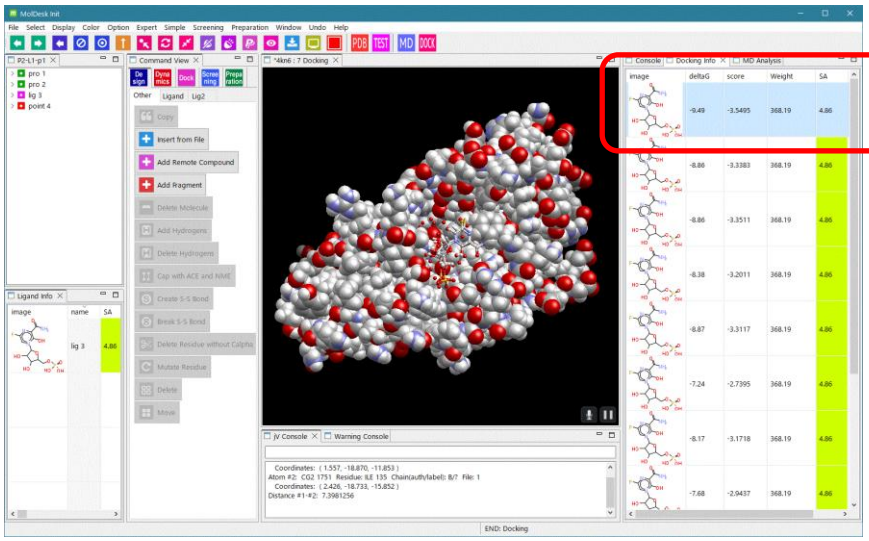
3.3. Confirmation of Results

When the docking calculation is completed, the Docking Info screen displays a list of the 10 molecular structures predicted by the docking calculation in order of best score.
The values of the molecular structure attributes are as follows

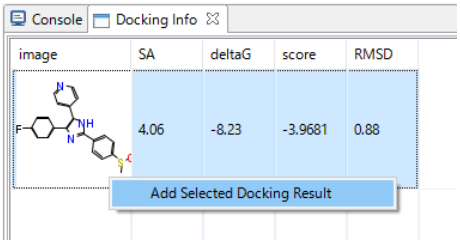
ΔG value (deltaG, free energy)

Score (score, docking score)

RMSD (value for the ligand used in the docking calculation input)



Clicking on a molecule in the Docking Info screen and clicking the ↑ ↓ keys will display the selected molecule one by one in the 3D screen.



Select a candidate structure in the Docking Info screen (Ctrl+click for multiple selections), right-click, and select "Add Selected Docking Result" to add the candidate structure to the Ligand Info screen, Add Selected Docking Result" to add the candidate structure to the Ligand Info screen. The result will be added to the calculation system and can be used for MD calculations, etc.

4. Saving and Loading Projects

4.1. [File] - [Save As]

Saves the displayed system with a project name. The command history is also saved.

Execute [File] - [Save As] and in the [Make PROJECT directory] dialog,
  select [Create New Folder] or [New Folder]
  or [New] - [Folder] from the right-click menu
and enter a folder name. This folder name will become the new project name.

All data (including command history) of the currently displayed system will be saved in the created folder.

[Please note that if you specify an existing folder without creating a new folder, the following folders and files will be output directly under the folder.
  original folder
  work folder
  cif and pdb files downloaded via internet

* If you are interested in the details of the files stored in the project, please refer to the MolDesk Basic Manual.

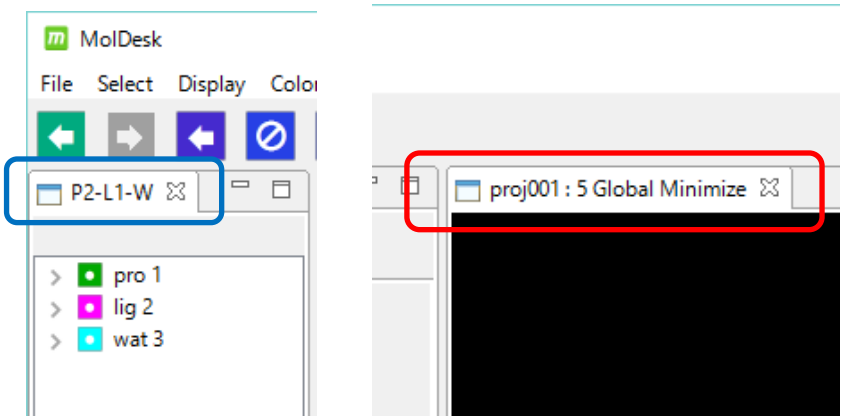
4.2. [File] - [Open Project]

Open a project that has been saved in the past via [File] - [Save As],
or
MoldeskProject00000
MoldeskProject00001
MoldeskProject00002
…
in the directory set in the Default Project Directory under
[Help] - [Preferences] - [8. Other].

Select the existing project folder (including “original” and “work” folders directly below) and click [OK].

The tab names on the tree display screen (blue box "P2- L1- W" in the figure below) indicate the number of proteins and compounds.
P indicates protein chain, L indicates compounds, W indicates the presence of crystal water, and M indicates metals and ions.
In the tree view, denotes protein, denotes compound, denotes water, denotes metal ion, and denotes sugar.

The last command is indicated by the tab name on the 3D screen ("proj001 : 5 Global Minimize" in the red frame in the figure below).
The tab name indicates [Project name : History number Execution command name].



Executed commands can be confirmed by clicking [UNDO] or [REDO].

5. 3D View of Molecular Structure

5.1. Mouse Operation

Rotate and move molecules on the 3D screen with the mouse.

Movement	Mouse Operation
X-axis (left/right axis) rotation Y-axis (vertical axis) rotation	Left drag
Z-axis (depth axis) rotation	Shift + right drag (left/right direction)
Move in X-axis (left/right) direction Move in Y-axis (up/down) direction	Right drag
Move in Z-axis (depth) direction (zoom in/out)	Shift + left drag Or, rotate the wheel

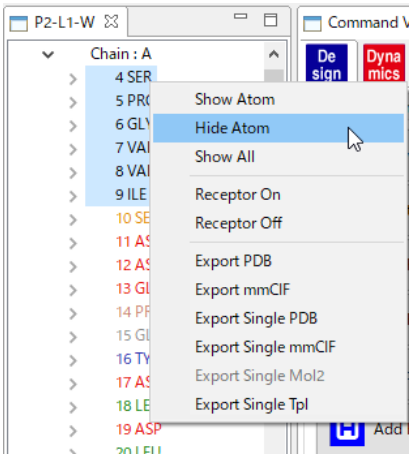
* For MAC, Left click = click

Right click = [Command] + click

5.2. Select molecule, chain, residue, atom

The selection of molecules, chains, residues, and atoms is performed with the mouse, but the operation differs between the 3D screen and the tree view screen.

Operation	3D Screen	Tree view screen
Multiple selection	Ctrl + click	Ctrl + click
Consecutive multiple selections	-	Shift + click
Select residues	Double click	Click residue name
Select Chain	Triple click	Click on chain name
Select molecule	-	Click on molecule name

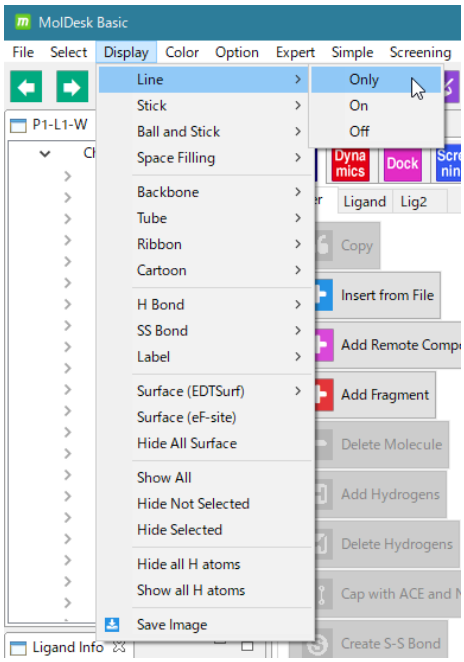


Multiple molecules, chains, residues, and atoms can be displayed or hidden together.

Select multiple molecules, chains, residues, and atoms in the tree view and right-click [Show Atom] or [Hide Atom].

Click [Show All] to show all residues and atoms.

5.3. Select a display model



By selecting a molecule, chain, residue, or atom, and then selecting a model from the [Display] menu, you can change the display model to Line, Stick, etc.

The meaning of the options are as follows

[Only] : Display only this display model in 3D.

[On] : Overlays this display model on other display models.

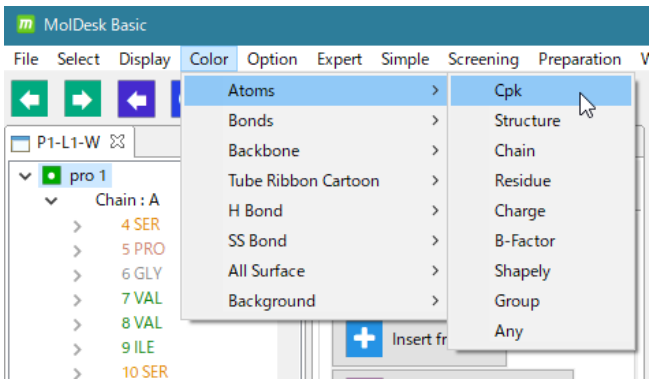
[Off]: Erase this display model.

For other display models, please refer to the following site of MolDesk

https://www.moldesk.com/moldesk-basic-commands/#Display

5.4. How to color

You can change the color of molecules, chains, residues, and atoms.



Select a molecule, chain, residue, or atom, and choose a color from the [Color] menu to change its color.

You can also change the color and transparency of all molecular surfaces at the same time by selecting [Color] - [All Surface].

For more information on each item in the [Color] menu, please refer to the following site of MolDesk.

https://www.moldesk.com/moldesk-basic-commands/#Color

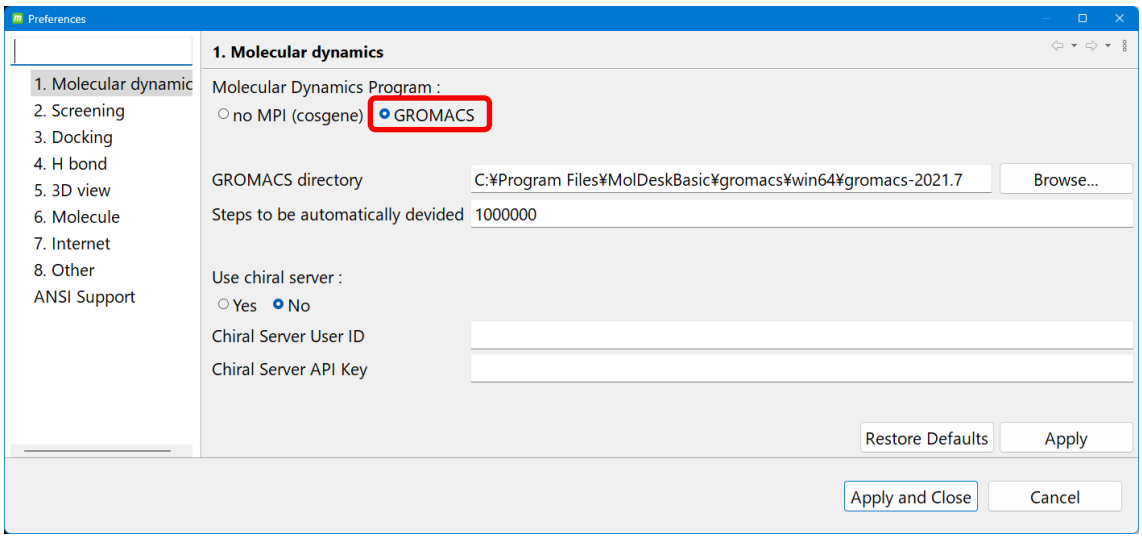
6. MD Calculations in GROMACS

6.1. [Preference] - [Molecular dynamics] settings

6.1.1. If [GROMACS] is selected

In the [Help]-[Preference]-[Molecular dynamics] screen, select [GROMACS] under [Molecular Dynamic Program :].

Performs energy minimization and MD calculations with GROMACS on a computer with MolDesk Basic installed.



On Windows 10 and Windows 11, this setting is not necessary since the GROMACS executable program is implemented beforehand.

On Linux and MAC, the user must install GROMACS and configure the [GROMACS directory] setting in the installed GROAMCS. The installation procedure is explained below.
https://www.moldesk.com/faq/faq16/

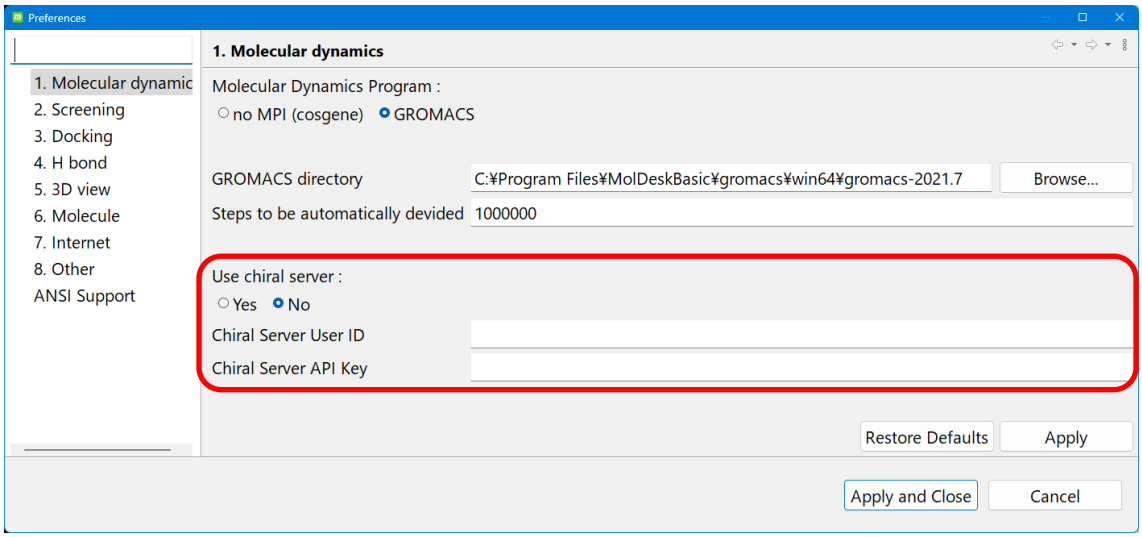
For [GROMACS directory], set the directory where **share** and **bin** exist.

* In the current version, GROMACS is executed in bin/gmx without specifying the number of parallelism.
  If bin/gmx does not exist in the installation directory, GROMACS cannot be executed.

The parallel number of OpenMP and thread MPI depends on the function of automatically specifying the parallel number of GROMACS.

6.1.2. If [Use chiral server=Yes] is selected

When Yes is selected for [Use chiral server :] in the [Help]-[Preference]-[Molecular dynamics] screen



The energy minimization and MD calculations are performed by GROMACS on the cloud server provided by Chiral. A separate contract between the user and Chiral is required.

Enter the [Chiral Server User ID] and [Chiral Server API Key] issued by Chiral.